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ENVIRONMENTAL SCIENCE FOR THE EUROPEAN REFINING INDUSTRY

Mineral Oil in FCM plastics
MOSH and MOAH
Brussels
April 20, 2018

Juan-Carlos Carrillo

(Shell, CONCAWE STF-33)

MOSH MOAH QUIZ

- How much MOSH is in FCM 95?
  - 5 – 10% ?
  - 0.5 – 1.0% ?
  - 100% ?

- MOAH found in articles is of concern:
  - Always
  - Depending of the structures
  - Depending on the levels

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Points of discussion

- What exactly is MOAH and MOSH?
- What are the procedures in refining to make sure MOSH and MOAH do not end up in plastic products?
- Natural versus artificial incidence of MOSH in articles?
- Are MOHs a REAL issue for plastic converters (besides those on the Positive list of 10/2011)?

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MOSH and MOAH – What is it?

Chromatography context:

Mineral Oil Saturated Hydrocarbons - MOSH:

The "unresolved complex mixture" of aliphatic hydrocarbons between C20 and C35, containing multibranched saturated and alkylated multiple ring naphtenic alkanes; the carbon numbers are defined by the elution range respectively the retention time of the corresponding n-alkanes in a gas chromatographic analysis on a dimethylpolysiloxane coated column.

- MOSH is an analytical fraction, not a substance on the market
- MOSH is used as a chromatographic measure of the alkane content of an oil
- These adverse health effects attributed to the MOSH fraction, come from animal studies on hydrocarbons that are extrapolated to humans
- In animal studies in different rat strains and dogs, only the F344 rat shows adverse effects to some type of oils and waxes.

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MOSH and MOAH – What is it?

Chromatography context:

Mineral Oil Aromatic Hydrocarbons -MOAH:

(Highly alkylated) aromatic hydrocarbons with carbon numbers between C20 and C35, of one or more aromatic rings; the carbon numbers are defined by the elution range respectively the retention time of the corresponding n-alkanes in a gas chromatographic analysis on a dimethylpolysiloxane coated column.

- MOAH is a fraction, not a substance on the market.
- MOAH is used as a chromatographic measure of the aromatic content of an oil
- It is considered as an indicator of the presence of unrefined petroleum based products
- The concern is based on the possibility that MOAH fraction containing 3-7 membered rings may be potentially carcinogenic

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Take Home Message MOSH and MOAH

- MOSH and MOAH are vague terms, their interpretation is highly contextual
- MOSH and MOAH analytical fractions do not correspond to petroleum products that are placed on the market
- These fractions may contain constituents coming from products of different degrees of refining and purity
- Furthermore, these fractions can also be found in products of other origin than mineral oil, for example, n-alkanes of natural origin found in fruits and vegetables
- MOSH and MOAH is contextual: impossibility of tracing their origin and the health risk they pose
  - MOAH can be harmless or of concern deepening on the origin.
- There are petroleum derived products that are lawfully used (e.g. cosmetic and food contact).
  - refined products are safe
  - presence of MOSH and MOAH is expected, unavoidable
  - no reason for suspecting non-compliance or health risk

The MOSH and MOAH "meaning" is subject of ***when***, ***what*** and ***how*** you use it.

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Mineral Oil / Wax Refinement

Manufacture of Mineral Oil and Wax

Impact on Substance Composition

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Mineral Oil – What is it?

- Generic term used to group several petroleum derived liquids with "oil-like" viscosity
- Manufactured by vacuum distillation of the residue from atmospheric distillation.
- ~ 40 substances (identifiers or CAS number) which could be regarded as "mineral oil" with boiling points from 300ºC to 700ºC.
- Differ in physical chemical properties (e.g. viscosity) and chemical composition (e.g. aromatic content).
- Because of thousands of isomers, MO can't be described with a single chemical formula.
- Mineral oils are described as *complex substances* of ***U**nknown or **V**ariable composition, **C**omplex reaction products or **B**iological materials*, or shortly **UVCB.**
- Mineral oil is matrix, a single entity, with its own intrinsic properties behaving as a (complex) substance.
  - hydrocarbon constituents follow a physical chemical pattern
  - varying according to crude oil
  - controlled manufacture,

- In the EU, by law "mineral oils" are UVCBs and not mixtures.
- A mixture are intentionally blended to achieve a certain composition.
- Mineral oil is a substance

- Hydrocarbon solvents have a different manufacturing process which distinguishes them from mineral oil, with their chain lengths up to C20.
- Because of this the MOSH-MOAH terminology does not apply to hydrocarbon solvents.

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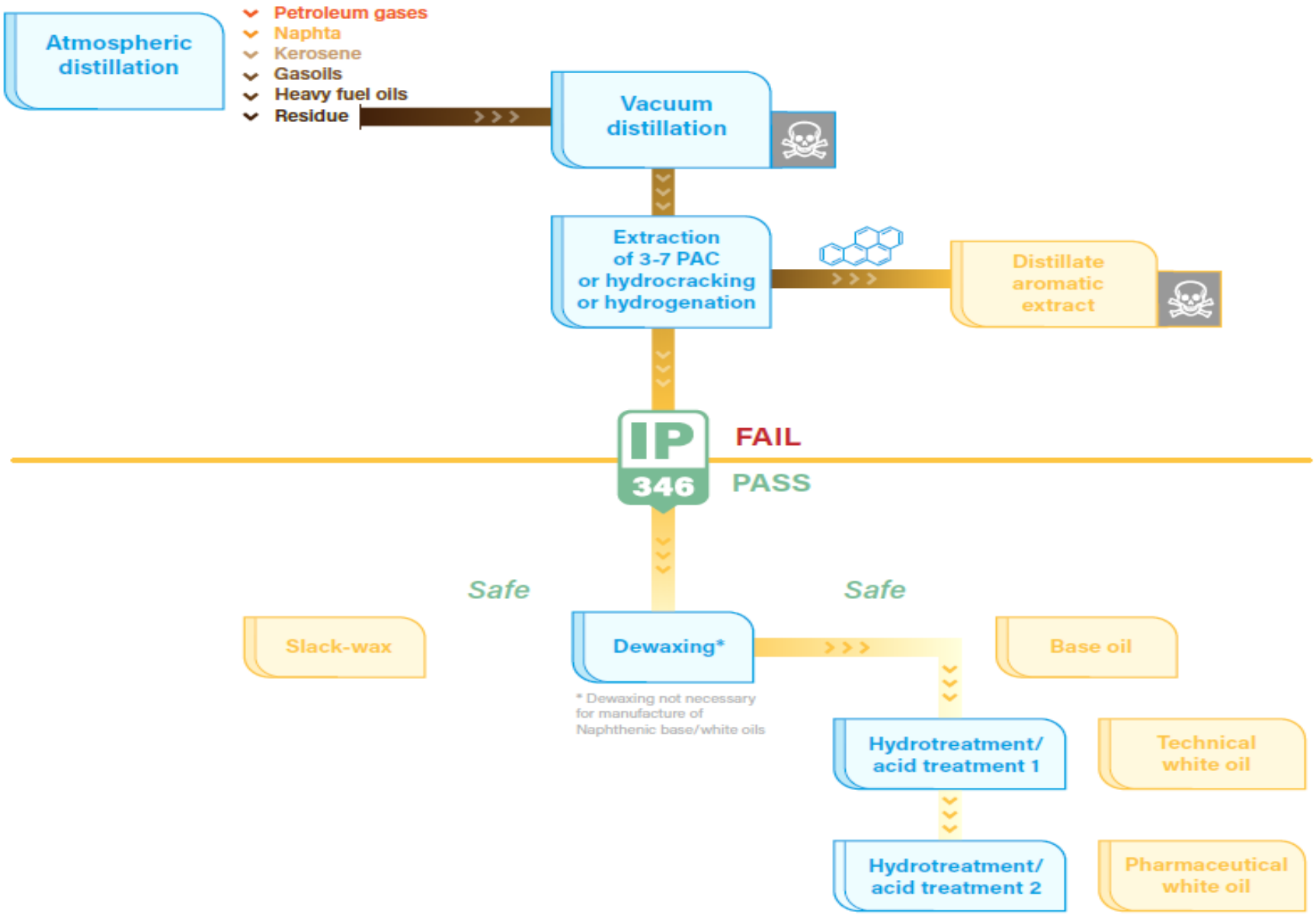
Pharmaceutical White Oil Manufacture



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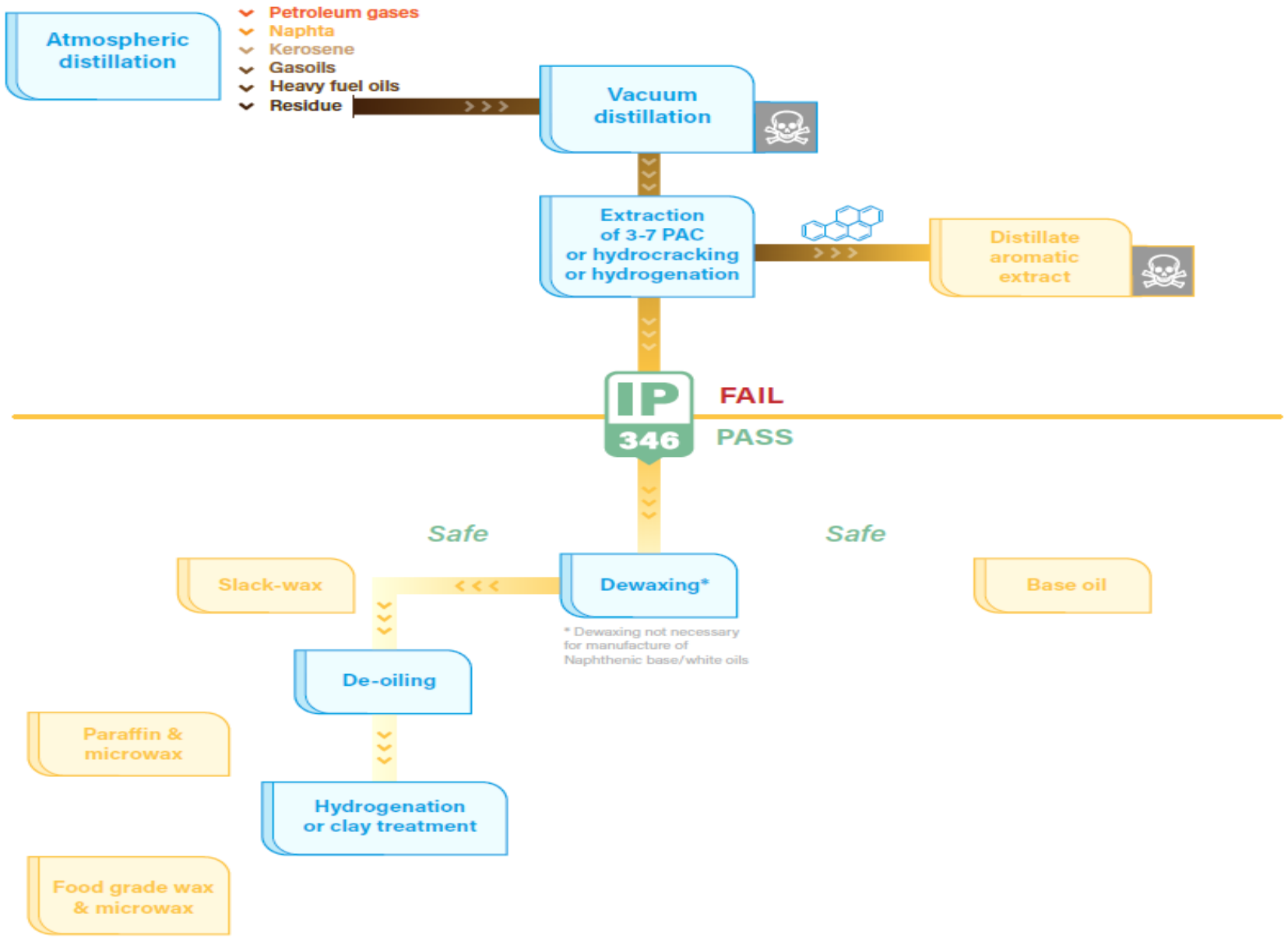
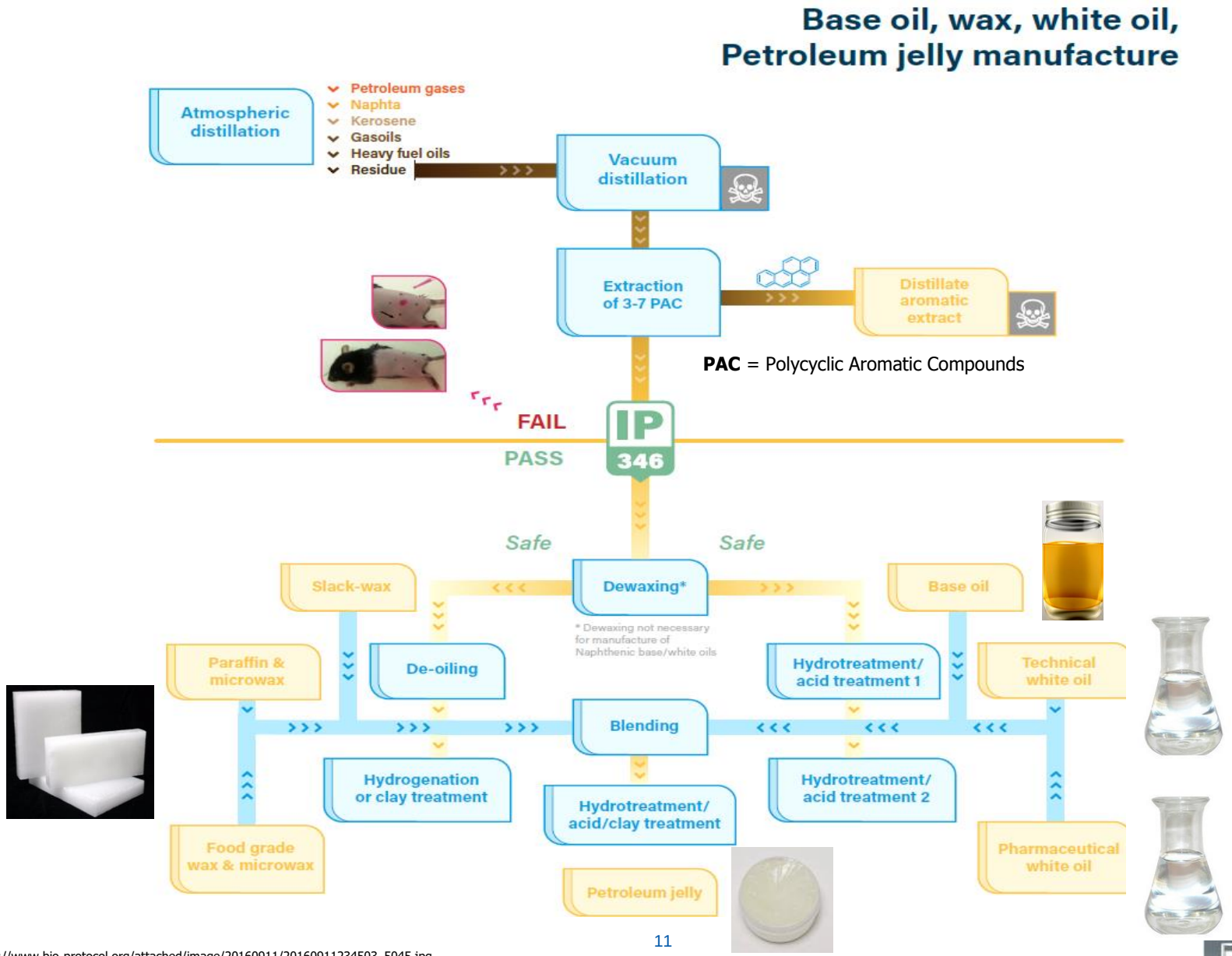
Paraffin and MicroWax Manufacture



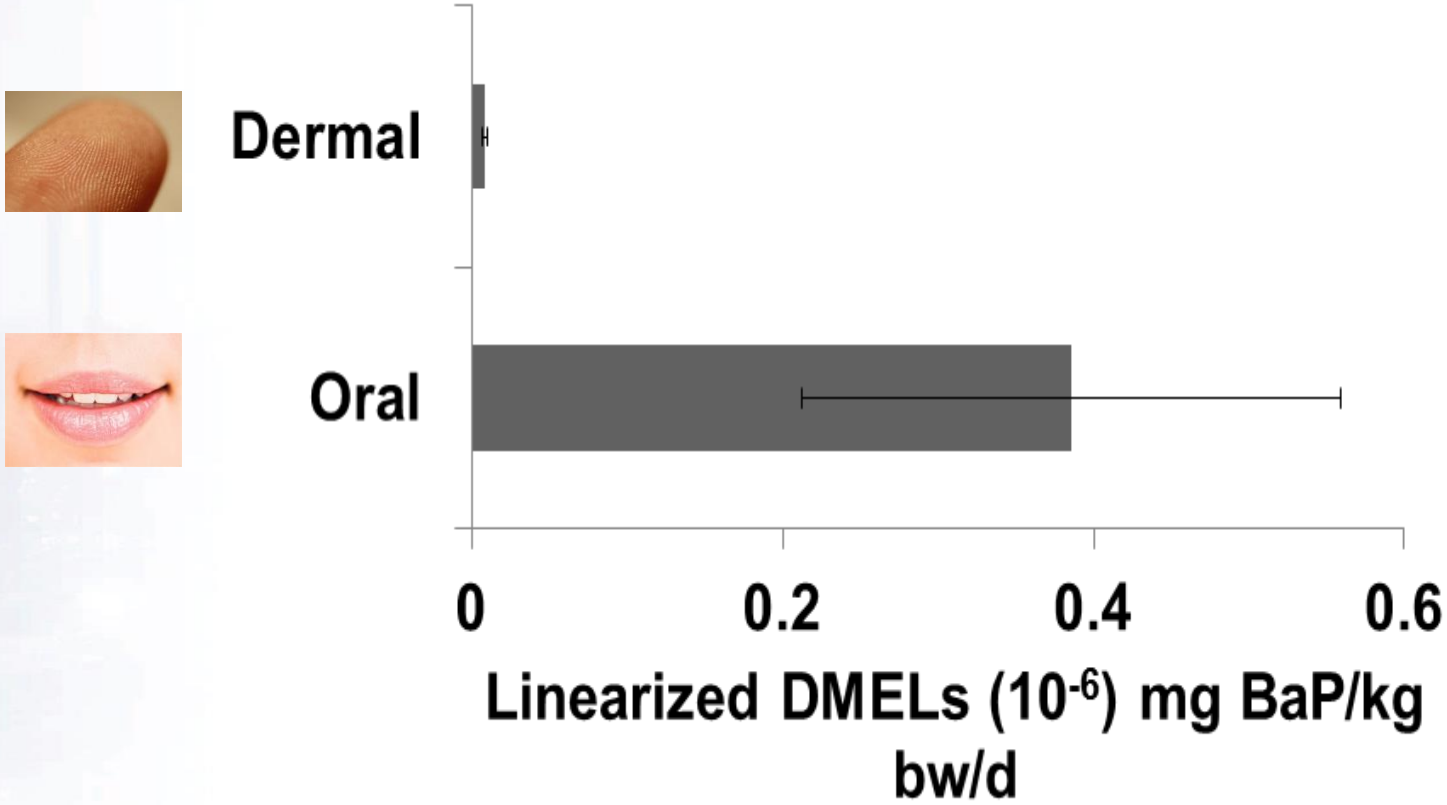
The Mouse Skin Painting Bioassay In Mineral Oil Manufacture



http://www.bio-protocol.org/attached/image/20160911/20160911234503_5045.jpg

Why the Dermal Route?

Based on Derived *Minimal* Effect levels (**DMEL**), the risk by dermal route is the worst case scenario for PAC mediated carcinogenicity: risk of **one in a million** in developing cancer at a certain dose level.



DMELs calculated from BMD_{10} values for BaP carcinogenicity tests in rodents.
See Table 61 of Baua Annex XV Restriction Report Proposal for a Restriction

Slide credits: D. Adenuga - ExxonMobil

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B[a]P Rodent Tumor Mode of Action Dictates Tumor Location

Key Event 1
Bioactivation to reactive metabolites

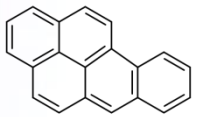
Key Event 2
Reactive DNA damage, formation of DNA adducts

Key Event 3
Fixing of DNA mutations

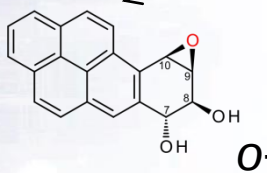
Key Event 4
Clonal expansion – proliferation of initiated tumor cells

Apical Event
Tumors

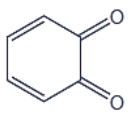
B[a]P



CYP1A1/1B1/1A2

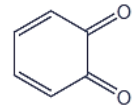


Epoxide



o-quinone

cation



Tissues rich in CYP activity – skin, liver etc.

Tumor promotion:
Local irritation, cytotoxicity, inflammatory response

Most sensitive tumor sites – dermal, oral (forestomach, oral cavity, GIT)

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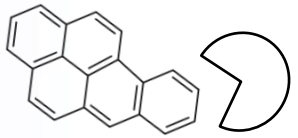
MOAH Molecular Structure Determines Carcinogenicity
Steric Hindrance

MOAH substrate

CYP enzymes



MOAH substrate

CYP enzymes

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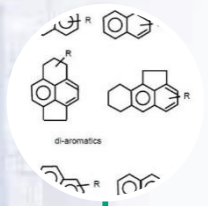
What Type Of MOAH Are Carcinogenic?



Two MOAH types

> 3 ring PAC

< 3 ring highly alkylated aromatics

Substance or fraction	Live animals after 40 weeks	Re-treatment of live animals with a tumour promotor
Carcinogenic oil	Tumours in all animals	-
Fraction I (PAC "free")	No tumours	No tumours
Fraction II (2 and 3 rings)	No tumours	No tumours
Fraction III (> 3 rings)	No tumours	Tumours in all animals
Fraction I+II+III	Tumours in all animals	-

1. *Agarwal et al., 1988*
2. *Doak et al.,1985*

To assess MOAH it is imperative to test SUBSTANCE (the actual oil), and NOT the isolated fractions.

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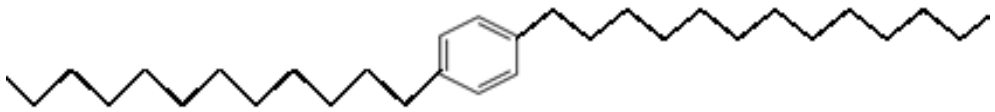
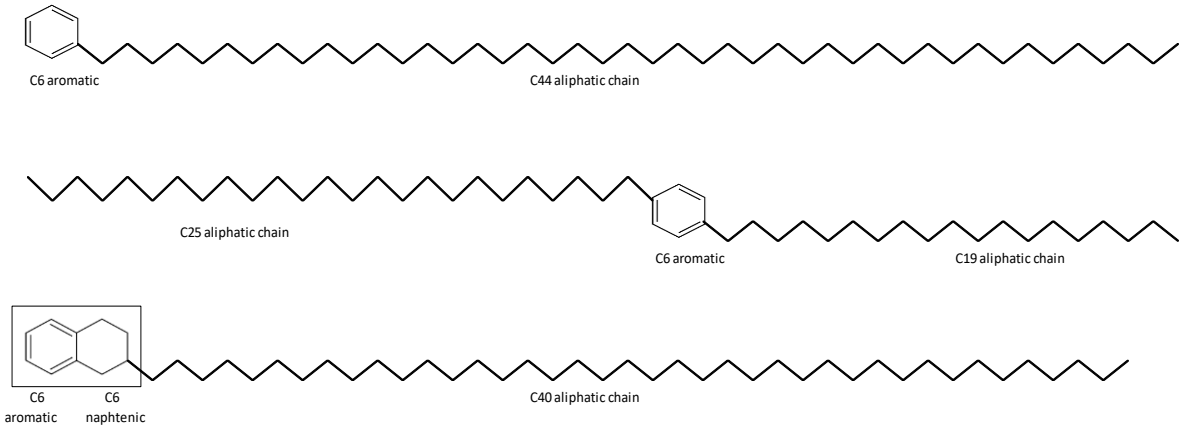


Interpretation of MOAH Measurements

Juan-Carlos Carrillo

Why Is MOAH "High"? – The MOAH Paradox
Example Microcrystalline Wax

- **MOAH (HPLC-GC FID) typical levels:**
  - 1-5 %.
- **MOAH content < C35**
  - virtually absent
- **Content of aromatic protons (NMR):**
  - ~ 0,1 – 0,5 %
- **Typical av. mol weight microwax:**
  - 700 (C50H102)
- **3-7 rings aromatics:**
  - trace levels (specific UV test / Grimmer etc.)



- High alkylation of a small number of aromatic carbons leads to high MOAH values (everything is interpreted as aromatic)
- The higher the MW the greater the MOAH

MOAH paradox: the more aliphatic, the more "aromatic"

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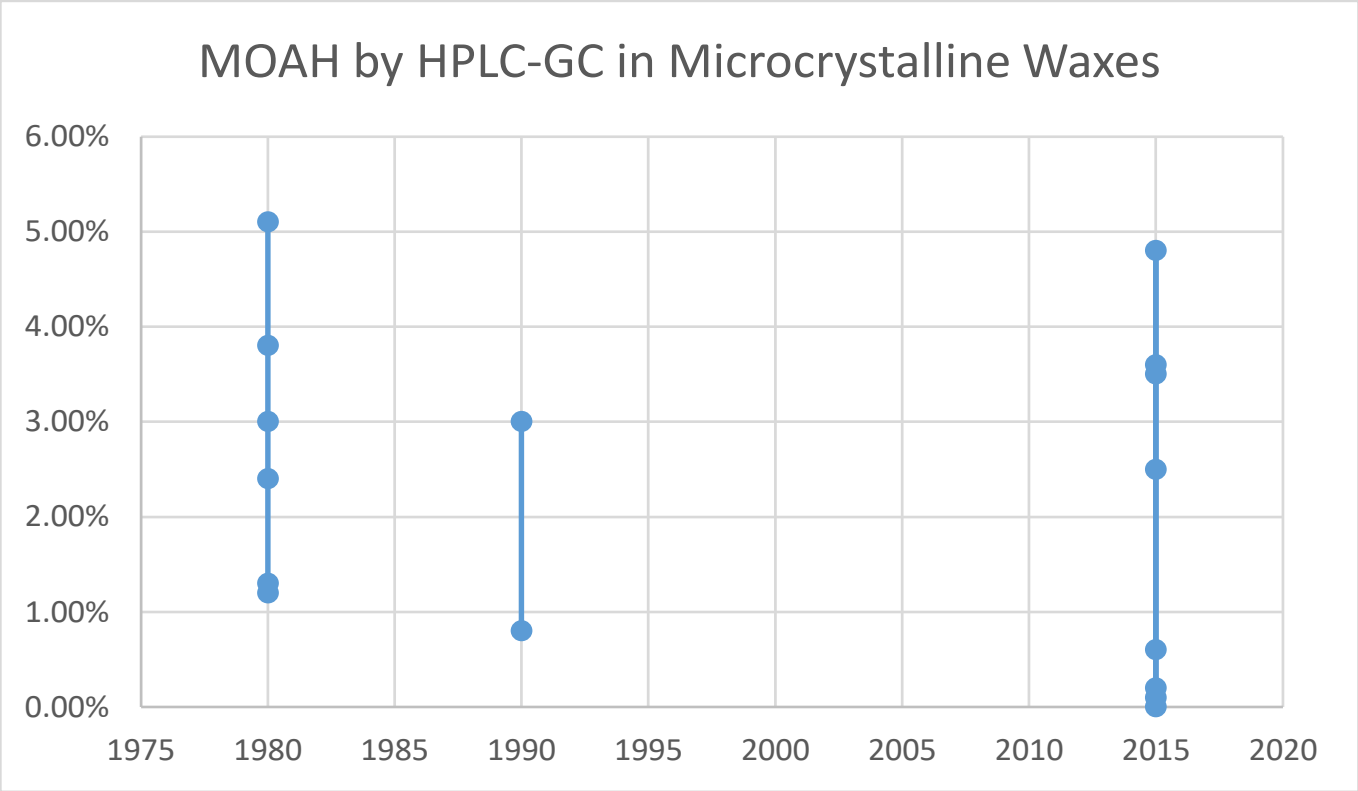
Former Material Is Representative For Today – Decades Long Consistency In Manufacturing

- Recent HPLC-GC measurements on old and new production samples of several (EU) manufacturers (2015) confirm that MOAH was always present – nothing new!
- Historic concentrations used for fundamental toxicological studies were at least as high or even higher than those in products presently on the market



- <1980 Concawe 84-60 Samples
- 1990 BIBRA Study Samples
- 2015 Recent production samples of several EU Manufacturers

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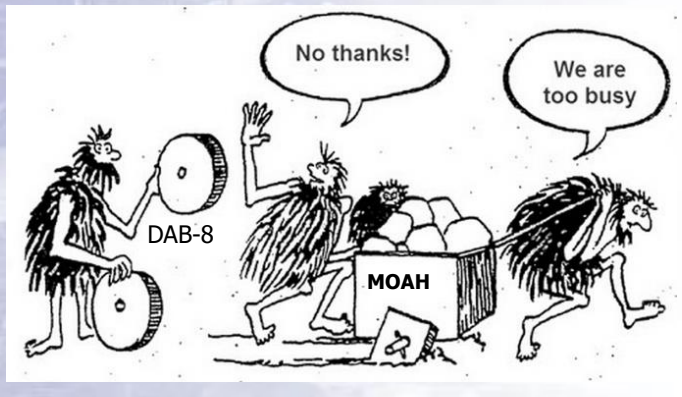
Do We Need A Sophisticated MOAH Method?

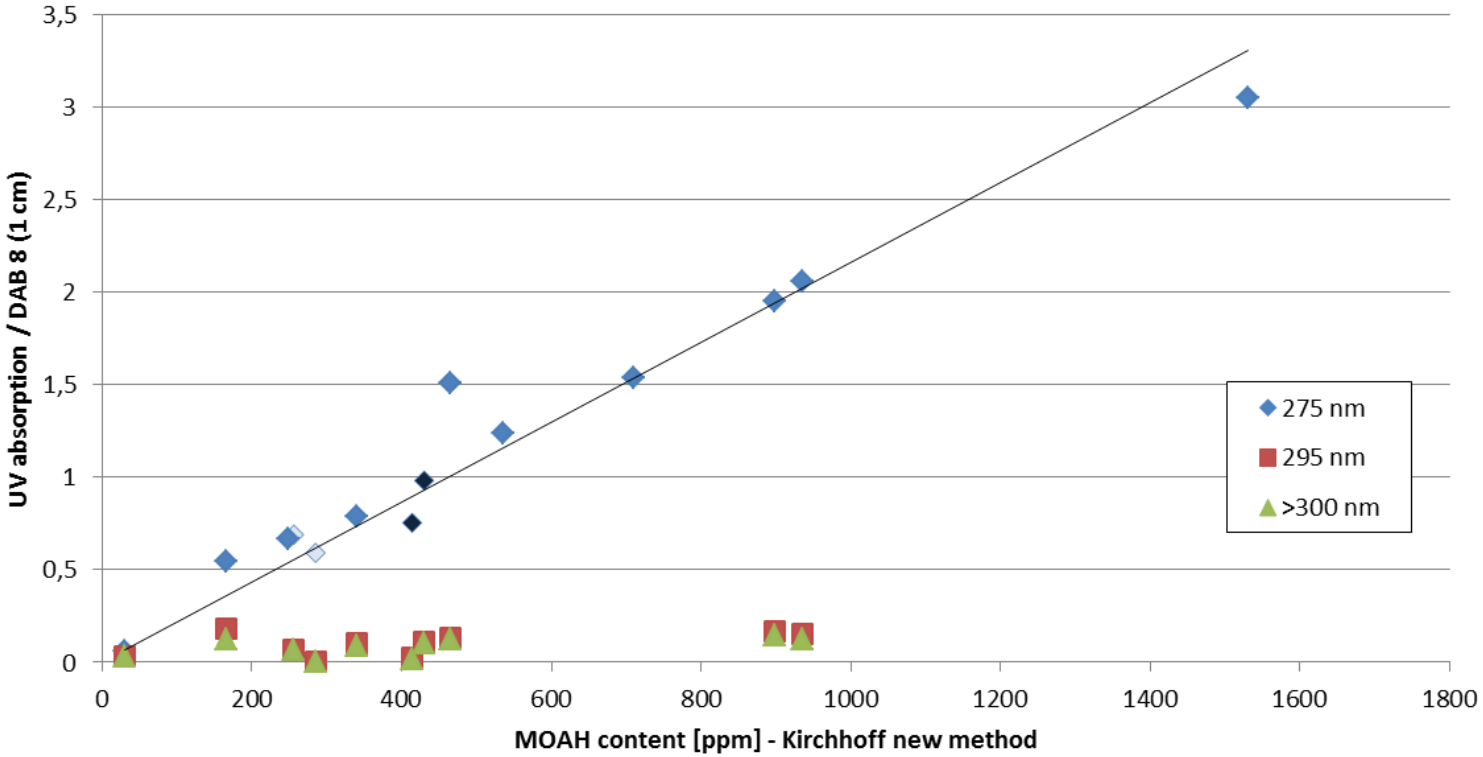
The measurement of Total Aromatics (MOAH) is nothing new

- **DAB 8 UV-method** did the same

Best correlation with Oils

- Oils have shorter MOAH`s
- Longer MOAH chains are not toxicologically relevant
- Replaced by UV-methods including DMSO extraction to focus on PAH
- not biased by MW





DAB 8 UV = Deutsche Arzneibuch 8, ultra violet method

Data source: H&R

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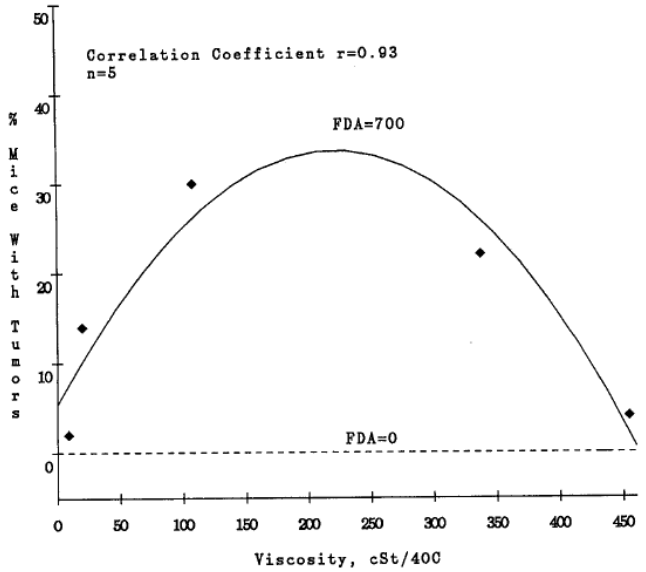
Factors that influence analytical methods

- Molecular structure (high vs low, or, no alkylation)
- Viscosity of the oil (linked to BP range)



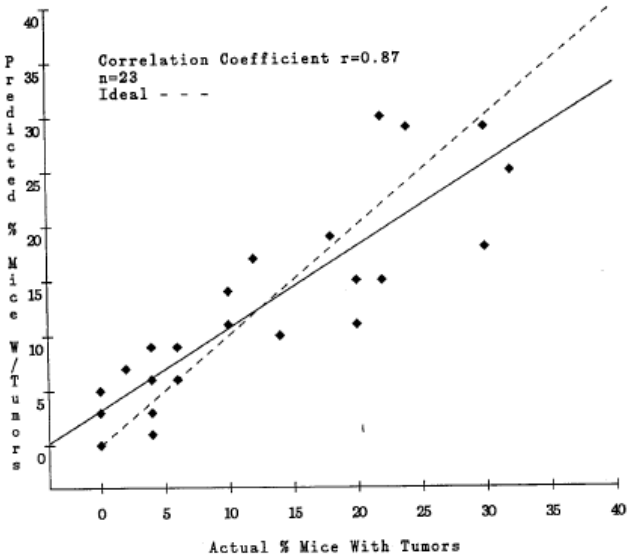


Figure 4 — Predicted percent mice with tumors *vs.* actual percent mice with tumors.

- Viscosity is an important property of an oil for hazard assessment
- MOAH – HLPC measurements are heavily biased by High MW (overprediction)
- MW corrections should be considered
- Absorbance of < 200 (at 280 nm), linked to MI < 1 and T% of 4% is indicative of negligible hazard.

Haas et al., 1987. Am Ind. Hyg. Assoc. 48(11)

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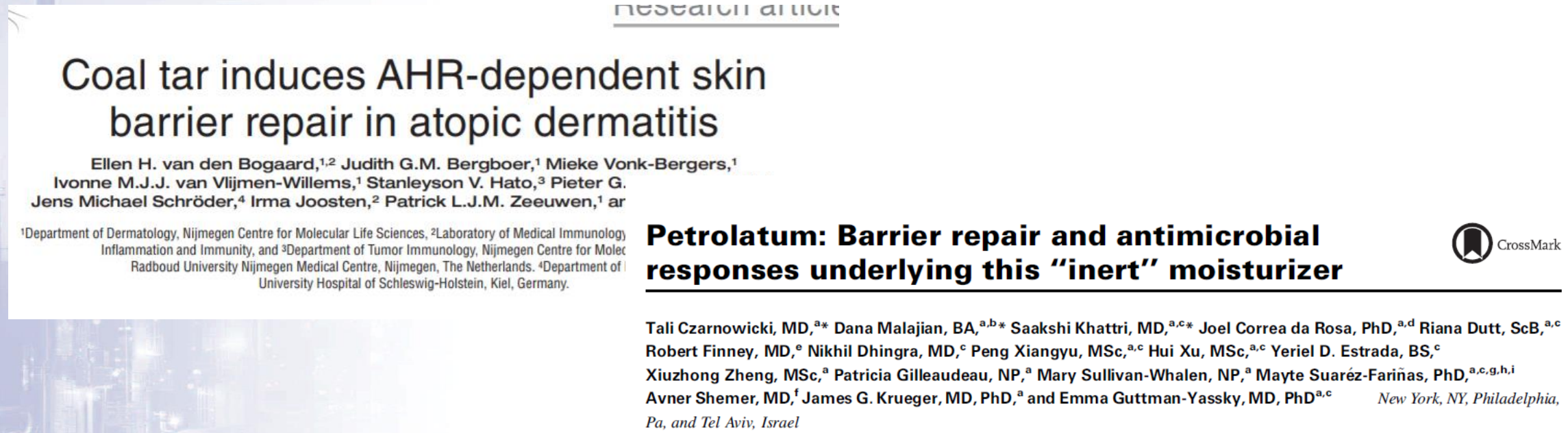
The "good MOAH"



Research article

Coal tar induces AHR-dependent skin barrier repair in atopic dermatitis

Ellen H. van den Bogaard,[1,2] Judith G.M. Bergboer,[1] Mieke Vonk-Bergers,[1] Ivonne M.J.J. van Vlijmen-Willems,[1] Stanleyson V. Hato,[3] Pieter G. Jens Michael Schröder,[4] Irma Joosten,[2] Patrick L.J.M. Zeeuwen,[1] ar

[1]Department of Dermatology, Nijmegen Centre for Molecular Life Sciences, [2]Laboratory of Medical Immunology Inflammation and Immunity, and [3]Department of Tumor Immunology, Nijmegen Centre for Molec Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. [4]Department of University Hospital of Schleswig-Holstein, Kiel, Germany.

Petrolatum: Barrier repair and antimicrobial responses underlying this "inert" moisturizer

CrossMark

Tali Czarnowicki, MD,[a]* Dana Malajian, BA,[a,b]* Saakshi Khattri, MD,[a,c]* Joel Correa da Rosa, PhD,[a,d] Riana Dutt, ScB,[a,c] Robert Finney, MD,[e] Nikhil Dhingra, MD,[c] Peng Xiangyu, MSc,[a,c] Hui Xu, MSc,[a,c] Yeriel D. Estrada, BS,[c] Xiuzhong Zheng, MSc,[a] Patricia Gilleaudeau, NP,[a] Mary Sullivan-Whalen, NP,[a] Mayte Suaréz-Fariñas, PhD,[a,c,g,h,i] Avner Shemer, MD,[f] James G. Krueger, MD, PhD,[a] and Emma Guttman-Yassky, MD, PhD[a,c] *New York, NY, Philadelphia, Pa, and Tel Aviv, Israel*

- There is some evidence that a certain type of MOAH is good for you…
- MOAH is thus highly contextual.

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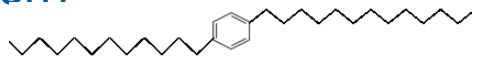
MOAH Take Home Message

- The term "MOAH" does not describe the quality of the substance, because there are two types:
  - Bad MOAH: 3-7 ring PAC (eliminated through refinement)

- Harmless /good MOAH: highly alkylated aromatics (what is left after 3-7 PAC elimination)



- Refinement, toxicologists and compliance tests (IP346, Pharmacopeia) focus on Bad MOAH: 3-7 ring PAC

- Refined mineral oil products have an impeccable history of safety: even if "MOAH" is present

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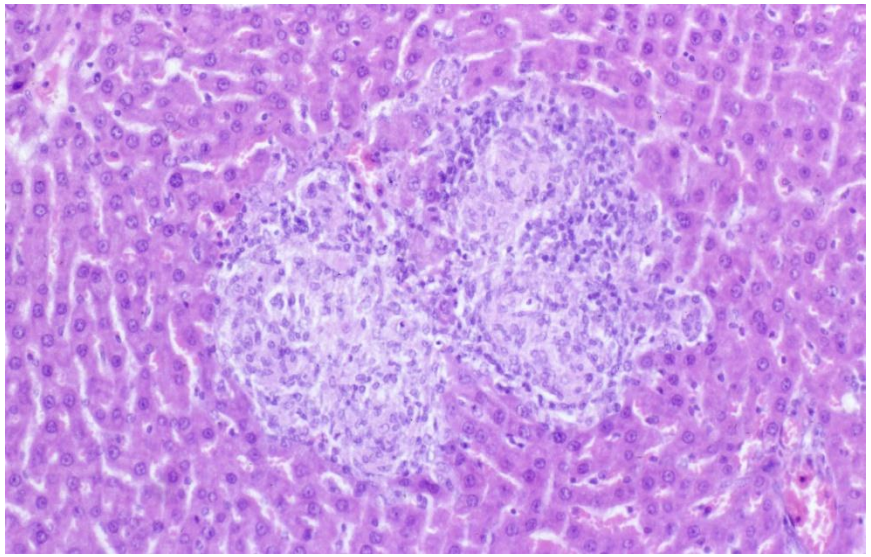
Interpretation of MOSH within Toxicology studies

Hepatic Granulomas Associated with MHC

- Subchronic feeding studies of MHC in Fischer 344 (F344) rats have shown a dose-related increase in histopathologic observations in some treatment groups.
  - Observations include granulomas and microgranulomas in the liver
  - Appear to result from an inflammatory response



- **These observations in F344 rats have not been observed in other rat strains**
- **The granuloma in F344 rats are not observed in humans**
  - **F344 → epithelioid granuloma**
  - **Human → lipogranuloma**

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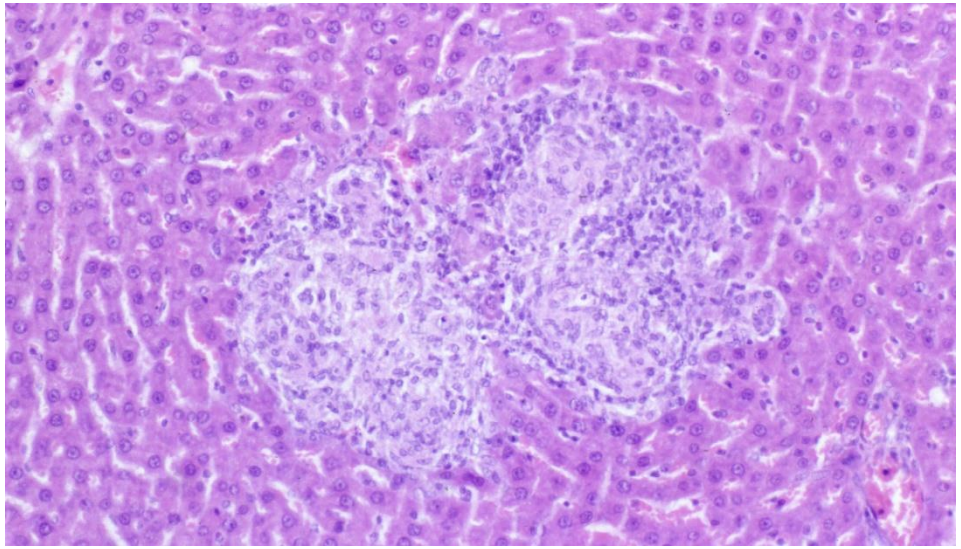
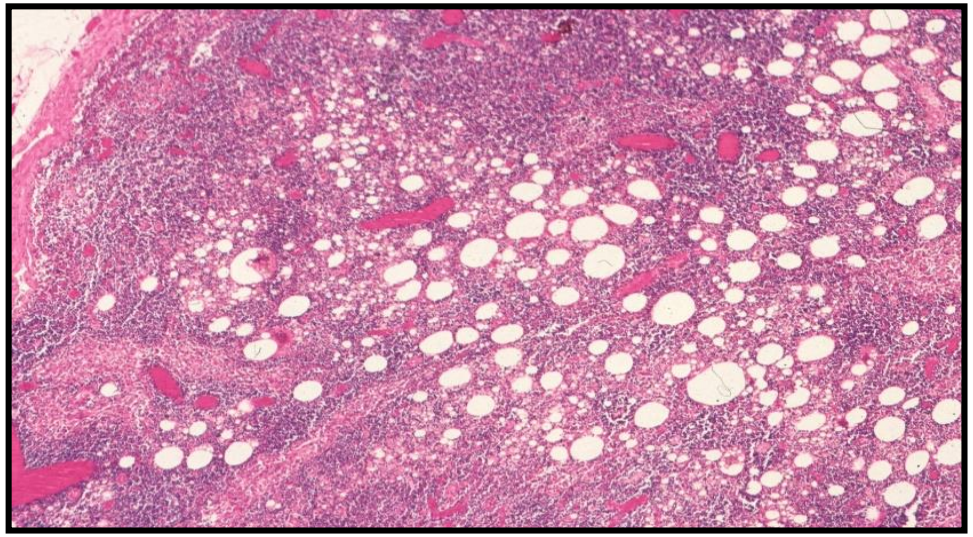
F344 hepatic granuloma are morphologically distinct from those observed in humans.

F-344 High Dose Liver
Epithelioid Granuloma



Human Autopsy
Lipogranuloma



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2012 EFSA Conclusions and Recommendations

- In rats, MOSH with carbon number higher than C_{16} can bioaccumulate and may lead to formation of microgranulomas in the liver and mesenteric lymph nodes (MLN). Microgranulomas in MLN are considered of low toxicological concern because they are not associated with an inflammatory response or necrosis, do not progress to adverse lesions and available studies did not show an effect on immune functions. In the liver, microgranulomas were associated with inflammatory reactions.

Most "potent" MOSH – extrapolated to oils

Table 17: NOAEL observed in female Fischer 344 rats exposed to waxes, based on MLN histiocytosis and liver microgranulomas.

Test item[1]	Physico-chemical properties	Duration	Concentration in diet (mg/kg)	Dose (mg/kg b.w per day)	NOAEL (mg/kg b.w. per day)		Reference
					MLN histiocytosis	Liver microgranulomas	
Waxes							
LMPW	Viscosity at 40 °C (mm^2/s): solid Viscosity at 100 °C (mm^2/s): 3.3 Average MW: 375 C number range: 19-42	90 days	20, 200, 2 000, 20 000	2, 19, 190, 1 951	< 2	19	Smith et al, 1996
IMPW	Viscosity at 40 °C (mm^2/s): solid Viscosity at 100 °C (mm^2/s): 6.3 Average MW: 450 C number range: 21-49	90 days	200, 2 000, 20 000	19, 190, 1 951	< 19	19	Smith et al, 1996
HMPW	Viscosity at 40 °C (mm^2/s): solid Viscosity at 100 °C (mm^2/s): 15.4 Average MW: 630 C number range: 22-80	90 days	20, 200, 2 000, 20 000	2, 19, 190, 1 951	1 951	1 951	Smith et al, 1996

[1]LMPW: Low melting point wax; IMPW: Intermediate melting point wax; HMPW: high melting point wax.

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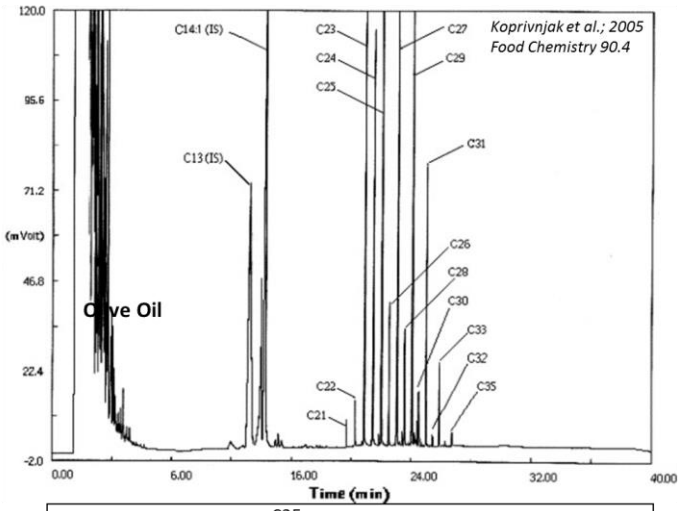
Natural n-Alkanes

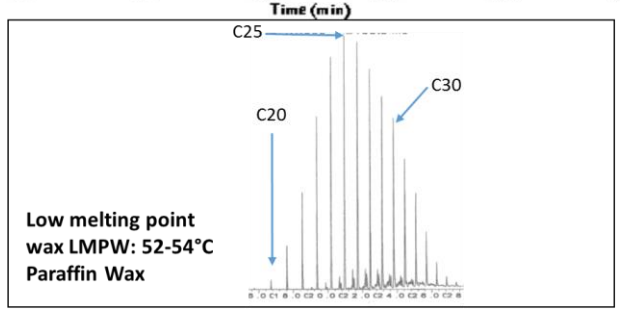
Number of samples	*Edible oil*	n-*alkane* (Σ_{15}^{33}) *content*[a] (*mg kg*$^{-1}$ *oil*)
6	Olive and extra virgin olive	28–99
5	Sunflower	105–166
4	Sesame	22–82
4	Vegetable	62–96
3	Corn	26–33
3	Walnut	7–30
3	Peanut/groundnut	27–40
1	Hazelnut	14
1	Sweet almond	44
1	Pistachio	21
1	Mustard seed	74
1	Safflower	61
1	Grapeseed	52
1	Olive and sunflower	100
1	Soya	17
1	Cod liver oil	16
1	Encapsulated cod liver oil	22
1	Encapsulated halibut liver oil	33
3	Specialist	
	barbecue	106
	for fish	49
	baking spray	11

n-Alkane content in edible oils
(McGill et al J. Sci Food Agri. 1993 ***61*** *357-362)*

- "Cuticular wax" coats external surfaces of most fruits and vegetables
- Composition: n-Alkanes, wax esters, fatty acids, ketones, fatty alcohols
- Typically carbon chain length 29 to 31 can be up to 50%
- Odd carbon number compounds dominate

A single apple: 25-50 mg n-alkanes/apple





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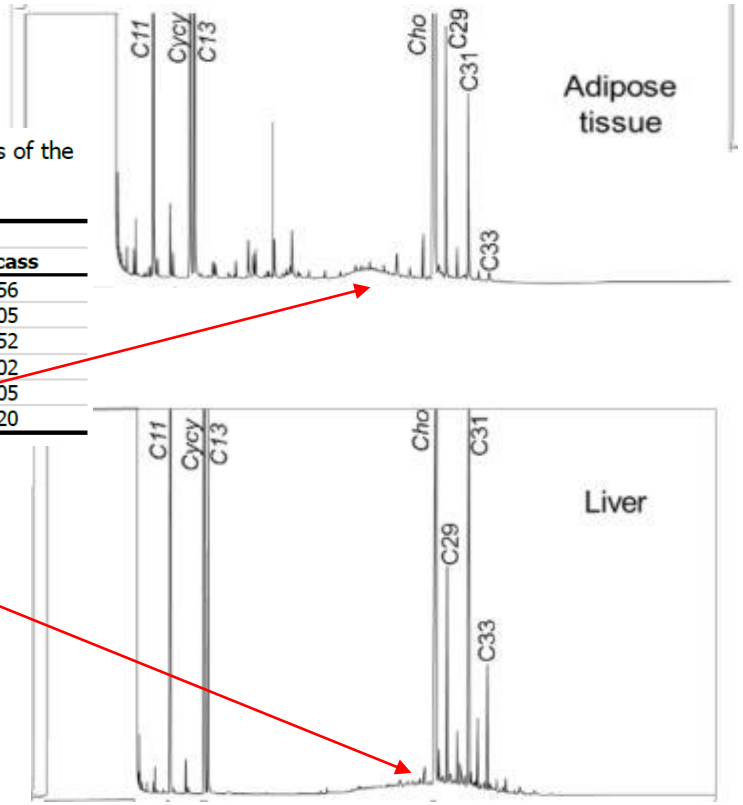
Accumulation of Natural n-Alkanes

Table 25: Concentrations (mg/kg) of the natural *n*-alkanes in the control feed and the tissues of the rats fed with the control feed

	Concentrations (mg/kg)				
	Feed	Liver	Spleen	Adipose tissue	Carcass
n-C_{29}	0.05	1.64	0.19	0.42	0.56
n-C_{30}	0.02	0.37	0.11	0.06	0.05
n-C_{31}	0.12	4.57	0.25	0.39	0.52
n-C_{32}	0.02	0.38	0.08	0.03	0.02
n-C_{33}	0.02	0.75	0.06	0.00	0.05
Total	0.22	7.72	0.70	0.89	1.20

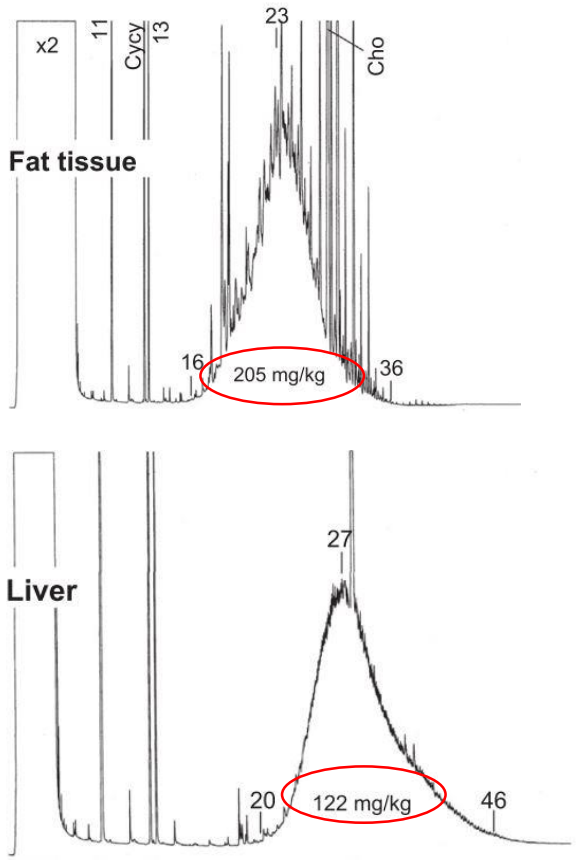
- The n-alkanes relationship in adipose tissue and liver is the inverse between F344 and humans

F-344 Data



EFSA Supporting Publication 2017:EN-1090; p 69

Human Data



Barp et al., 2014 Food Chem. Tox.; p 316

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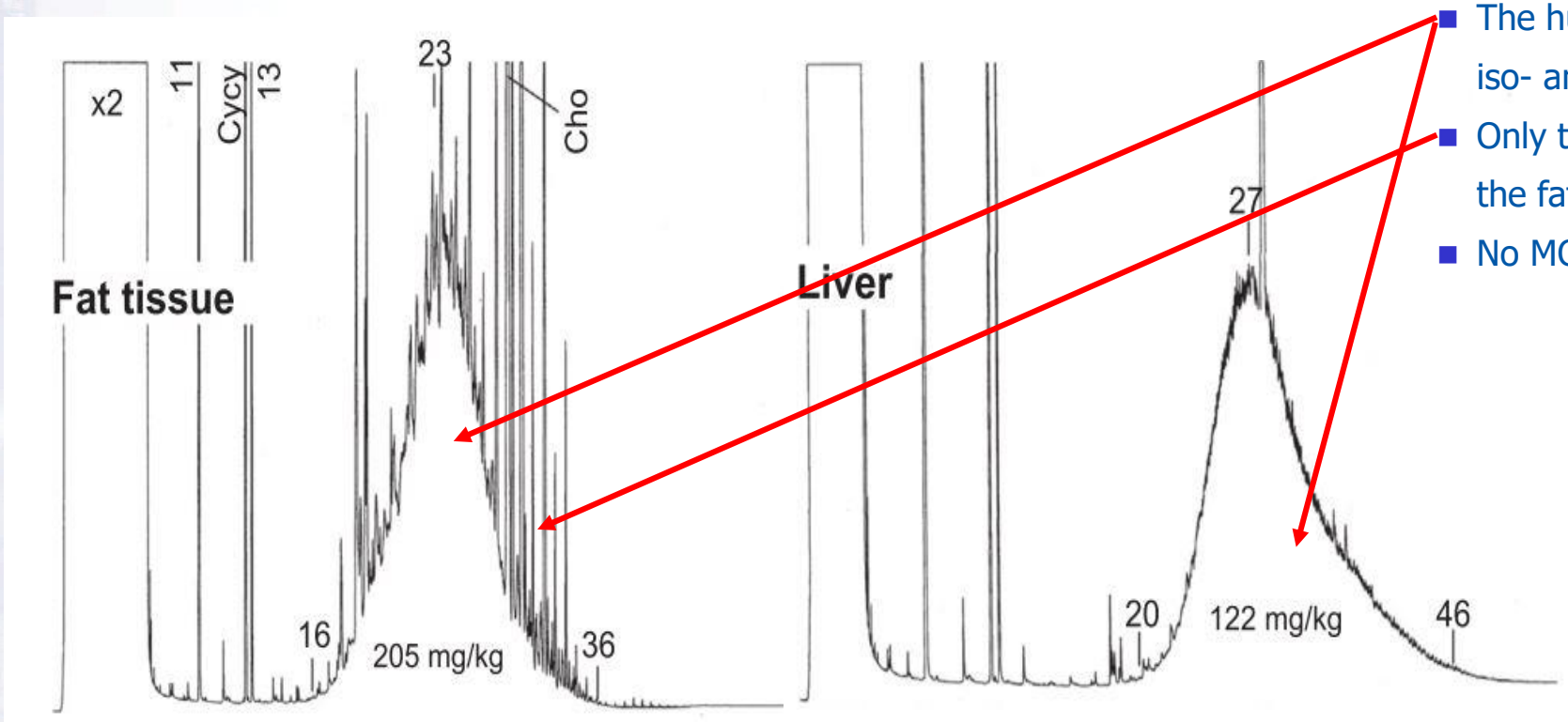
In humans MOSH levels in the fat proves that <u>there is exposure</u>



- The hump is the sum of iso- and cycloalkanes
- Only transient n-alkanes in the fat, non in the liver
- No MOAH in neither

Barp et al., 2014 Food Chem. Tox

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Lipogranuloma in humans – incidence and hydrocarbon levels

Analyses of Mass Spectrometric Data on Saturated Hydrocarbons from Two Cases Compared to Similar Analyses of Mineral Oils

Saturated Hydrocarbon Types	Composition (percent) #34135 (liver)	#34226 (spleen)	Mineral Oils*
Alkanes (normal & branched)	27.9	39.3	12.7 - 48.1
Cycloalkanes			
Non-condensed	25.7	18.8	21.3 - 26.0
Condensed			
2 rings	25.3	16.2	14.1 - 21.1
3 rings	11.4	11.5	7.4 - 18.3
4 rings	7.1	11.3	5.0 - 15.0
5 rings	2.6	2.9	2.0 - 8.4
6 rings	0.0	0.0	0.0 - 3.2

Cruickshank; 1984. Human Path.

Correlation of Extent of Oil Droplets in Liver and Speen with Saturated Hydrocarbon Content as Estimated by Thin-Layer Chromatography*

Oil Droplets Liver			Saturated Hydrocarbons (mg/gm of tissue)	Oil Droplets Spleen		
0	1+	2+		0	1+	2+
6	0	0	< 0.2	4	0	0
3	5	1	0.2 - 1.0	0	0	0
0	0	3	> 1.0	0	0	4

- Lipogranuloma although not adverse, it is associated with retention of mostly cycloalkanes
- No correlation between tissue hydrocarbon levels and proportion of n-alkanes
- indicative of transient presence of n-alkanes
- Lipogranuloma formation has a MOSH threshold
  - 0.2 mg/g tissue internal dose.

Saturated Hydrocarbon Content** (mg/gm of Tissue)	Oil Droplets Absent	Present	Incidence of Oil Droplets
< 0.2	31	0	0%
0.2 to 1.0	27	27	50%
1.0 to 2.5	2	34	94%
> 2.5	0	35	100%

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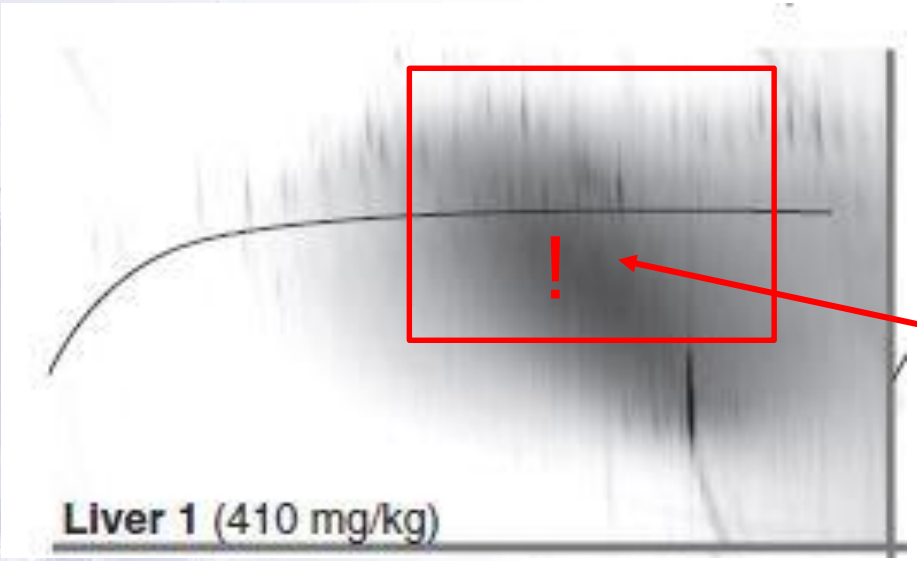
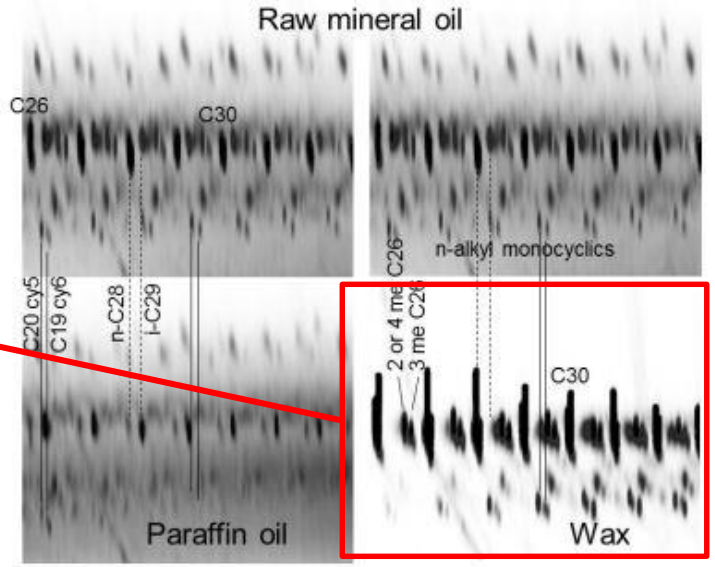
Lipogranuloma in humans - composition

Source: Bidermann et al. 2014. Science Total Env.



Source: Cravedi et al. 2017 EFSA ESR



- Humans are exposed to mineral oil and waxes, which have different compositions
- A requirement for lipogranuloma formation is the retention of the relevant hydrocarbons (e.g. cycloalkanes)
- In human livers containing saturated hydrocarbons no hydrocarbon wax constituents are observed
- The substances that are present "grey cloud" found in human livers are not present in waxes
- Waxes don't contribute to the perceived "MOSH" problem

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Fischer Lessons

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FCM
Mineral Oil and Waxes
Regulatory overview

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White Oils for Food Applications Regulations and Specifications

Application	Example	EU Regulation	US Regulation
Food Additive	Glazing agent, anti-foaming, carriers, preservative for eggs or dried fruits	EU 1333/2008/EC (Directive 95/2/EEC): **White Oils not on positive list**[1]	21 CFR 172.878
Processing Aid	Release agent/lubricant, dedusting agent in grain, pan oil, demoulding oil	**No EU Directive Some** specific **local regulations**[2]	21 CFR 172.878 (not differentiated from food additives)
Food Contact Materials	Extender oil in plastics, elastomers, paper, glass, metal, wood, cork, textiles, adhesives, pigments …	Framework (EC) 1935/2004 **Plastics: EU 10/2011** Others: to be developed Some local regulations[3]	Various FDA chapters Require mineral oils that meet 21CFR178.3620 (a),(b) or (c) purity
Lubricant for incidental food contact	Formulation of lubricants for food machinery	**No EU regulation**	21 CFR 178.3570 (requires 178.3620(b) oils) NSF H-1 registration

- Most existing purity requirements are based on PACs using UV-DMSO methods

(1) Microcrystalline waxes are listed as E 905
(2) Eg French Arrêté for "Auxiliaires technologiques" (Food Processing Aids) – 21 Oct 2006 – demoulding uses (biscuits)
(3) Germany: BfR recommendation XXV Purity requirements for mineral oil (155 BGA Mitteilung), microcristalline wax and paraffin

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EU Plastics Regulation 10/2011 – Food Contact

General requirements outlined in Art. 3 of EU framework Regulation (EC) N° 1935/2004 for materials and articles intended to come into contact with foodstuff.

Products permitted for the use in plastics for food contact applications

White mineral oils	FCM 95	Viscosity not less than 8,5 mm²/s at 100°C Carbon number amount <C25, max 5 % Average molecular weight not less than 480
Microcrystalline wax	FCM 94	Viscosity not less than 11 mm²/s at 100°C Carbon number amount <C25, max. 5% Average molecular weight not less than 500
Paraffin wax*	FCM 93	Viscosity not less than 2.5,mm²/s at 100°C Carbon number amount <C25, max 40% Average molecular weight not less than 350

* Restriction: 0.05 mg/kg food
Not to be used for articles in contact with fatty foods

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EU Plastics Regulation vs JECFA/EFSA ADI

- EFSA and JECFA have set ADIs to various oil categories (food additive use)
- EU Plastic regulation specifies oils and waxes that meet EFSA/JECFA categories
  - No direct regulatory link between EFSA/JECFA ADIs and the Plastic regulation

JECFA/EFSA Categories Specifications and ADIs	ADI JECFA	ADI EFSA	Kinematic viscosity at 100°C (cSt)	Average molecular weight	Carbon number at 5% boiling point	EU 10/2011 Plastic Regulation
Microcrystalline wax	0-20 mg/kg	0-20 mg/kg	≥ 11	≥ 500	≥ 25	X
Paraffin wax	-	-	≥ 2.5	≥ 350	Max 40% C<25	X
Mineral oil (high viscosity)	0-20 mg/kg	0-12 mg/kg	> 11	≥ 500	≥ 28	X
Mineral oil (medium and low viscosity) Class I	0-10 mg/kg	0-12 mg/kg	8.5-11	480-500	≥ 25	X
Class II	- (removed)	- (removed)	7.0 – 8.5	400-480	≥ 22	
Class III	- (removed)	- (removed)	3.0 – 7.0	300-400	≥ 17	

ADI : Admissible Daily Intake

- Some local regulations have set same oil requirements as EU Plastics Regulation, even if for different materials than plastics
  - e.g. German Draft Ordinance on Printing Inks, Elastomerleitlinie (Leitlinie zur hygienischen Beurteilung von Elastomeren im Kontakt mit Trinkwasser), Swiss Ordinance 817.023.21 April 2010 for food contact

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Hydrocarbon Waxes in the (Food Contact) Plastics Regulation EU 10/2011 : specifications and purity

EU 10/2011	FCM 93			FCM 94	
Description	**Waxes,** paraffinic, refined, derived from petroleum based or synthetic hydrocarbon feedstocks, **low viscosity**			**Waxes**, refined, derived from petroleum based or synthetic hydrocarbon feedstocks, **high viscosity**	
Specification	**Average Mol weight > 350 Dalton. Viscosity 100 °C > 2,5 cSt. Hydrocarbons with Carbon number less than 25, < 40 %.**			**Average Mol weight > 500 Dalton Viscosity 100 °C > 11 cSt Hydrocarbons with Carbon numb less than 25,<5 %**	
Typical Products covered	Mineral paraffin wax and synthetic (low viscosity) paraffin wax (both **foodgrade)**			**Mineral microcrystalline wax and synthetic** (high viscosity) paraffin wax (both **foodgrade)**	
Source	Vacuum distillate **mineral** oil		**FT process**	Residu vacuum distillate **mineral** oil	**FT process**
Abbreviation	**LMPW**	**IMPW**	LMSP	**Micro**	HMSP
Carbon distribution	**C20 - C35**	**C25 - C45**	**C20 - C50**	**C35[(3)] - C80**	**C30 - C90**
N-alkane content (%)	85-90	50 - 70	> 90	10 - 60	> 90
Melting point (°C)	52 - 60	60-68	50 - 100	50 - 100	110
Viscosity 100 °C (cSt)	3	7	3 - 8	11 - 30	8 (120 °C)
Average Mol weight	350	475	360 - 550	600 - 700	600 - 700
SML	0.05 mg/kg	0.05 mg/kg	0.05 mg/kg	None	None
Purity requirments	Based on absence PAH	Based on absence PAH	Based on absence PAH	Based on absence PAH	Based on absence PAH
MOAH by GC (%)	Virtually absent	Virtually absent	Virtually absent	0 - 7	Virtually absent
MOAH by NMR (%)	Virtually absent	Virtually absent	Virtually absent	0 - 0,5	Virtually absent

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Hydrocarbon Waxes in Annex 1 of EU 10/2011

FCM 93	FCM 94
Waxes, paraffinic, refined, derived from petroleum based or synthetic hydrocarbon feedstocks, low viscosity	Waxes, refined, derived from petroleum based or synthetic hydrocarbon feedstocks, high viscosity
Average molecular weight no less than 350 Dalton	Average molecular weight no less than 500 Dalton
Visocity at 100°C not less than 2.5 cSt	Visocity at 100°C not less than 11 cSt
Content of hydrocarbons with Carbon Number less that 25, not more than 40% (w/w)	Content of hydrocarbons with Carbon Number less that 25, not more than 5 % (w/w)
SML: 0.05 mg/kg	None
Not to be used for articles in contact with fatty foods for which similant D is laid down	

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Impact on the Listing of LMPW in Annex 1 of the Plastics Regulation

- Current situation
  - SML of 0.05 mg/kg creates problems:
    - Customers have identified some LMPW applications that result in higher SML values
    - Restrictions to use in contact fatty foods hurts general use in the plastics industry

Because Hydrocarbon waxes show no "MOSH-like" concerns

- EWF Action Plan
  - Prepare and submit dossier to obtain higher or no SML for Paraffin Wax
    - Relevant 90 days studies with Sprague-Dawley rats are available
    - No accumulation of n-alkanes in human livers
    - Dossier and supporting evidence is ready
    - Migration testing currently underway
    - Dossier submission plan for early Q2 2018

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90 Day Studies on White Oils

Table 16: NOAELs observed in female Fischer 344 rats exposed to white mineral oils, based on MLN histiocytosis and liver microgranulomas.

Test item identification: P indicates a paraffinic white oil, mainly containing branched alkanes, no or minor amounts of aromatics. N indicates a naphthenic white oil, mainly containing cyclo alkanes, no or minor amounts of aromatics. The following number indicates the approximate viscosity (expressed in mm^2/s) at 40 °C. The letter between brackets indicates the refining method applied (A: acid treatment; H: hydrogenation treatment). OTWO: oleum treated white oil (acid treatment), containing alkanes and cyclo alkanes, minor amounts of aromatics. HTWO: hydrotreated white oil, containing alkanes and cyclo alkanes (cyclo-alkanes in higher proportions than OTWO), no or minor amounts of aromatics.

Test item	Physico-chemical properties	Duration	Concentration in diet (mg/kg)	Dose (mg/kg b.w. per day)	NOAEL (mg/kg)		Reference
					MLN histiocytosis	Liver granulomas	
N10(A)	Viscosity at 40 °C (mm^2/s): 13.3 Viscosity at 100 °C (mm^2/s): 3.1 Average MW: 320, C number range: 15-30	90 d			2	190	Smith et al, 1996
N15(H)	Viscosity at 40 °C (mm^2/s): 16.6 Viscosity at 100 °C (mm^2/s): 3.4 Average MW: 330 C number range: 17-30				< 2	190	Smith et al, 1996
P15(H)	Viscosity at 40 °C (mm^2/s): 15. Viscosity at 100 °C (mm^2/s): 3. Average MW: 350 C number range: 18-30				2	190	Smith et al, 1996
	Viscosity at 40 °C (mm^2/s): 14.8	90				< 161	Firriolo et al., 1995
OTWO	Viscosity at 40 °C (mm^2/s): 26	90 days		, 440, 940,	0.93	46[2]	Baldwin et al. 1992
N70(A)	Viscosity at 40 °C (mm^2/s): 76.4 Viscosity at 100 °C (mm^2/s): 7.9 Average MW: 410 C number range: 21-35	90 days	20, 200, 2 000, 20 000	2, 19, 190, 1 951	2	190	Smith et al, 1996
N70(H)	Viscosity at 40 °C (mm^2/s): 68.0 Viscosity at 100 °C (mm^2/s): 7.6 Average MW: 420 C number range: 22-37	90 days	20, 200, 2 000, 20 000	2, 19, 190, 1 951	2	190	Smith et al, 1996
HTWO	Viscosity at 40 °C (mm^2/s): 69	90 days	10, 100, 500, 5 000, 10 000, 20 000	0.93, 9.0, 45, 450, 940, 1 800[1]	45	45[2]	Baldwin, 1992

Oils have their own data set and liver NOAEL (even if based on F344).

No reason to read across from Wax.

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MOSH and Low and Medium Viscosity Mineral Oil

- Oils should be evaluated on their own data set → not as surrogate of wax
- It is the liver and not the MLN the basis for this evaluation
- Only the F344 (and not the SD or human) shows adverse granulomatous effects
- In the F344 rat the NOAEL is 190 mg/kg bw
- In the SD the NOAEL is at least 10x higher. > 2000 mg/kg bw
- An ADI can thus be justified at > 20 mg/kg

- There is thus no reason to believe that low and medium viscosity oils can't be supported via a new ADI.

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Acknowledgements

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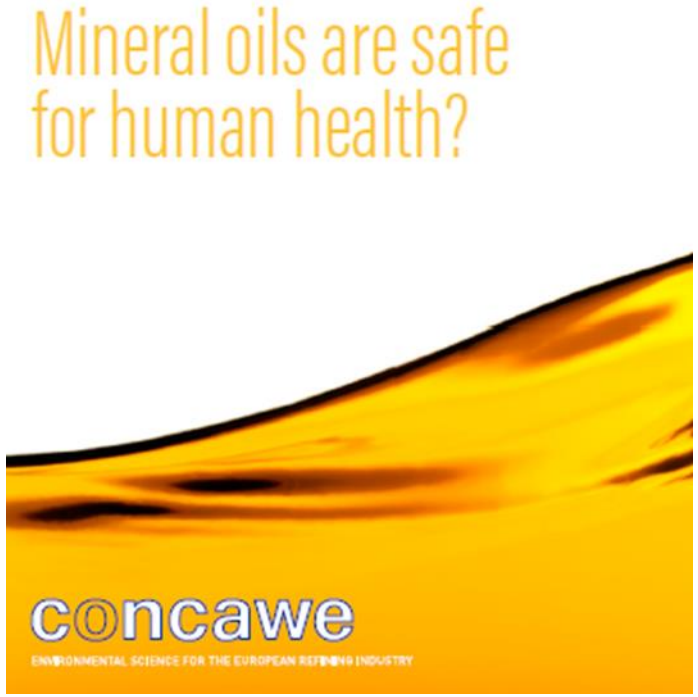
STF 33- CONCAWE



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Thank You

BACK UP

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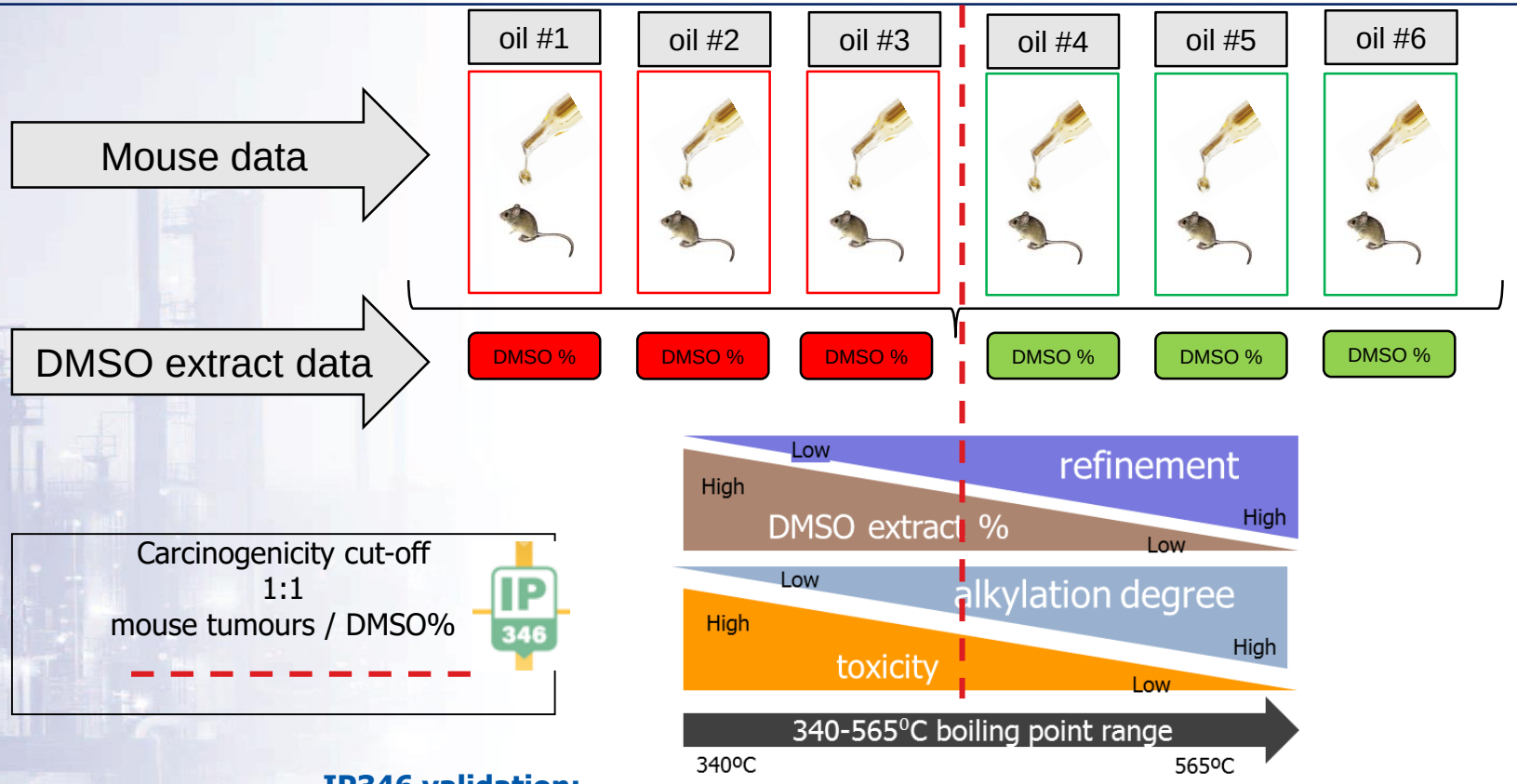
IP346: The Mouse Dermal Bioassay vs. DMSO% PAC Affinity



Carcinogenicity criteria for validation:

- No discrimination between benign or malignant tumours
- Potency (time of appearance of first skin tumour) is not considered
- Tumour incidence (4%) and not tumour formation stages used for IP346 validation

IP346 validation:

- DMSO-based screening method validated with animal data
- 1:1 relationship same oil mouse skin painting studies and its own DMSO-extract
- Determine a "cut-off": % DMSO extract that is correlated to non-carcinogenic oil
- **Cut-off solely on a hazard basis**:
  - Pass/fail in carcinogenicity assessment
  - Pass/fail is binary. "*Pass*" means **safe** (and not safer, safest, etc…)

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IP346 And Mouse Skin Painting Studies – Data Base

- **133 data** pairs support the IP346
- Completely eliminated carcinogenicity testing on animals
- Adopted in the 90's in the EU and in other countries (e.g. Australia, Malaysia) as regulatory standard for carcinogenicity assessment

- **It is the only validated analytical method with biological significance**

IP 346 < 3% oil is not carcinogenic
IP 346 ≥ 3% is carcinogenic

Reference	Data points (2 year studies)
CONCAWE 6/16 CONCAWE 94/51	**133 *** 104
Chasey et al., 1993	94
McKee et al., 1989	9
Doak et al., 1983 and (1985)	12 (6)
Blackburn et al., 1996	120
Roy et al., 1988	39

Negative predictivity = 95%

Accuracy = 89%
(because of false positives)

*Including all studies cited, without repetitions

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PAC UV-absorbance relationship to mutagenic activity

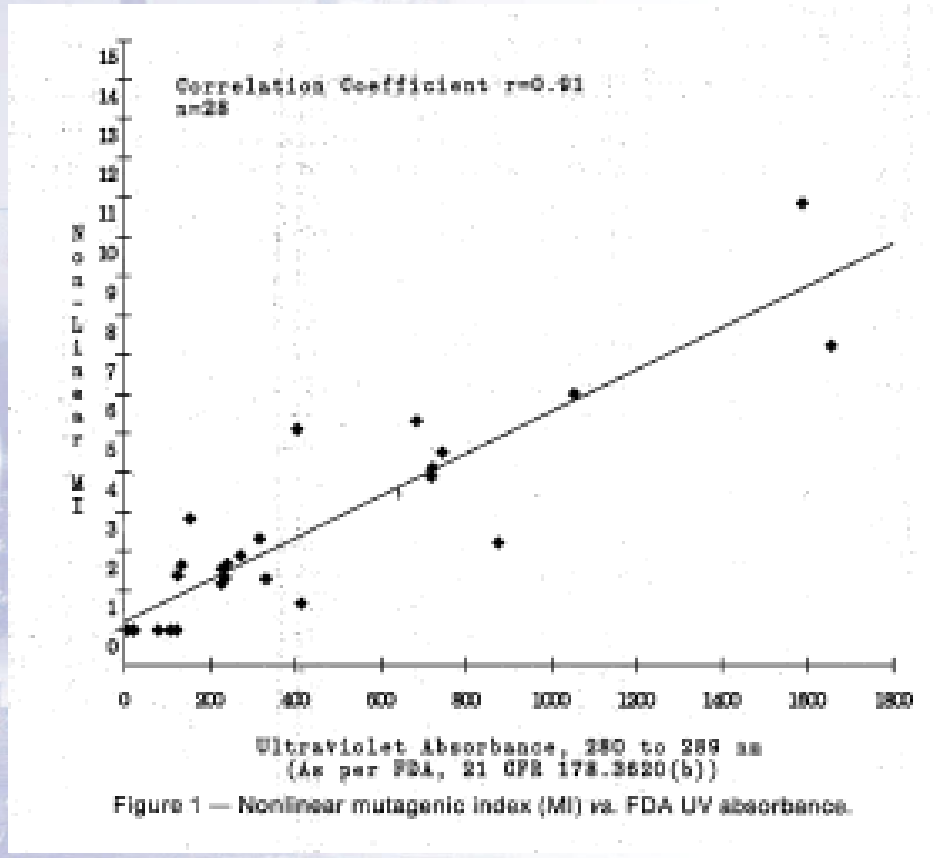

Figure 1 — Nonlinear mutagenic index (MI) vs. FDA UV absorbance.

Haas et al., 1987. Am Ind. Hyg. Assoc. 48(11)

- UV test with a DMSO extraction step (FDA 178.3620(b)
- MI index based on DMSO extracted PAC (ASTM E-1687/10)
- Absorbance at 280nm ~ 200 and MI < 1, indicates low risk of carcinogenicity (4% tumor incidence)

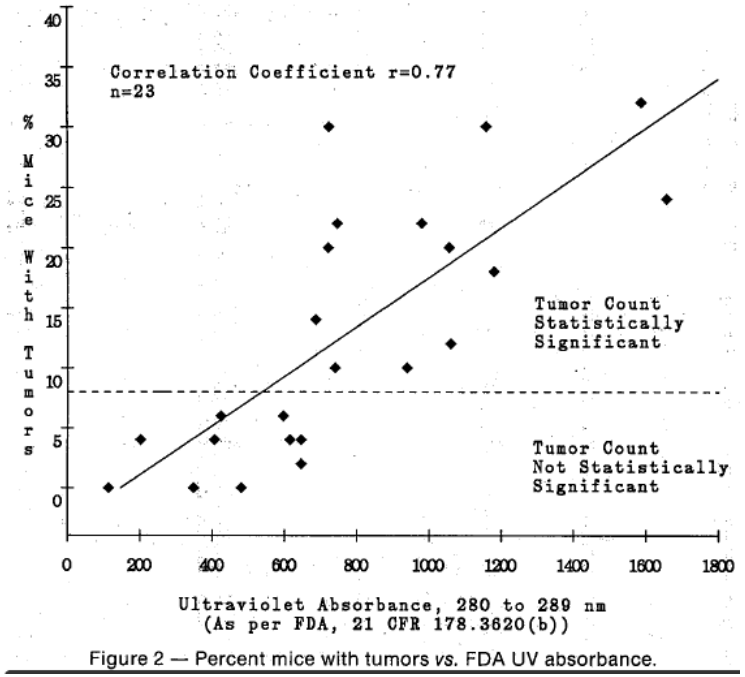

Figure 2 — Percent mice with tumors *vs.* FDA UV absorbance.

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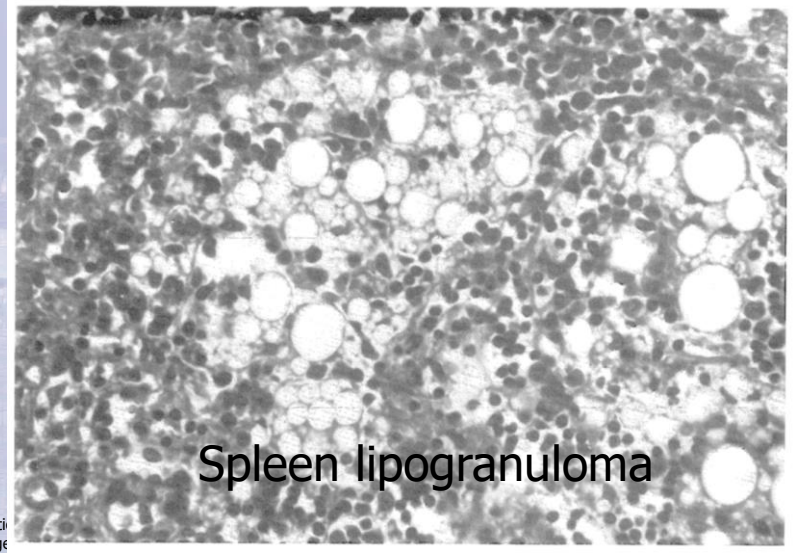
Lipogranuloma in humans - incidence



- **Lipogranuloma has no pathological consequence**
  (Fleming 2017, 1998)
- Lipogranuloma incidence in spleen (probably also liver) has geographical variation
  - Incidence: USA, UK, France, Australia, S. Africa, Venezuela
  - Nil incidence: Greece, Mexico, Argentina, East Africa, Japan, India

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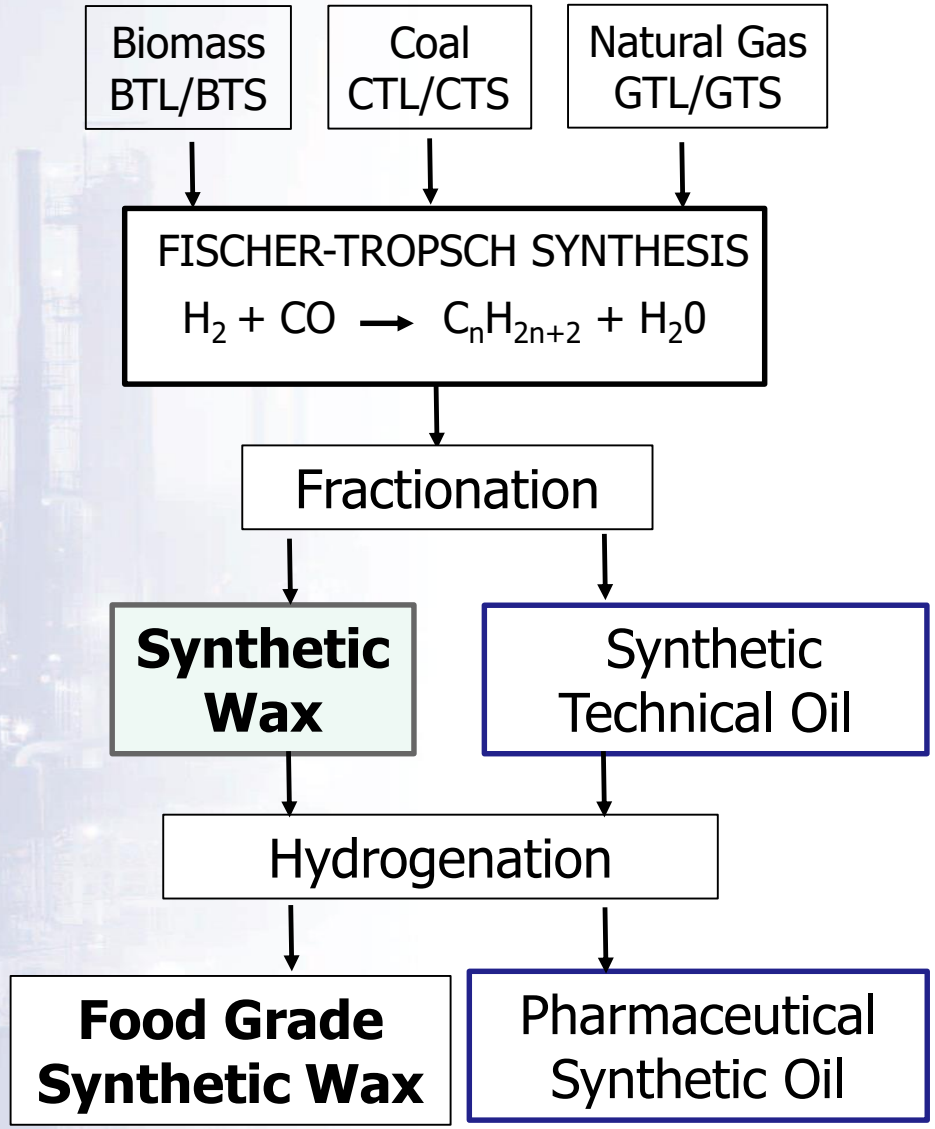
Carlton et al., 2001. Exp Toxic Pathol
Cruickshank; 1984. Human Path.

Synthetic Wax and Oil Manufacturing (Fischer Tropsch)



- Process invented in 1925 by Franz Fischer and Hans Tropsch
- Uses several carbon sources
  - Biomass to Liquids/Solids
  - Coal to Liquids/Solids
  - Gas to Liquid/Solid
- Manufactures a variety of products
  - Diesel, Naphta, Jet Fuel, Base Oils, Waxes, etc
- Commercial product range **includes oils** of different viscosities **and low and high melting waxes**

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Legislative framework – Paraffins and Microwax

	Food Contact Legislation		Food Additive		Pharmacopeia	Cosmetic	Pharmacopoeia and Cosmetic
Product	Regulation	Purity test	Regulation	Purity test	Regulation		Purity Criteria
Hard Paraffin/ Microcrystalline	FDA.178.3710	FDA 172.886	US Petroleum Wax Monograph FDA 172.886	FDA 172.886 (PCA -UV Absorption)			
	EC-1935/2004	Framework regulation					
	EC-42/2007 (Regenerated Cellulose film)	< 2 mg/dm2					
	Bfr - Recomendations for Paraffin: XXI, XXXV, XXXVI, XLIV, XLVIII, LII.	Bfr - Recomendation XXV					
Hard Paraffin	EU 10/2011 (PLASTIC), German Elastomer Guidance, Swiss Ordinance 817.023.21	95858 LVP			Eur /Ph- 9.0 USP -40	EC/1223-2009 and Cosmetic Europe recommendation	PAH Level (< 1/3 of absorbance of a solution containing 7 ppm naphtalene in DMSO at 278 nm)
Microcrystalline		95859 HVP	JECFA (CODEX: INS-905); EU 95/2 (E-905)	EC-231/2012	Eur /Ph- 9.0 USP -40 (*)	EC/1223-2009 and Cosmetic Europe recommendation	PAH (FDA 172.886)
	Bfr - Recomendations: XXI, XXV,XXXV, XXXVI, XLIV, XLVIII, LII					Colipa Recommendation nº 14	PAH Level (EC-1223/209) and (KV ≥ 11, MW≥ 500, Carbon number at 5% boiling point ≥25)

(*)- Microcrystalline Monograph in progress for European Regulation

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Hydrocarbon Waxes as Food Contact Materials - Regulations

Hydrocarbon Waxes as Additive or Formulation Ingredient		Waxes as FCM Group (EC 1935/2004) Framework Regulation
Harmonized FCM	**Non-Harmonized FCM (Member State Legislation)**	**Non-Harmonized FCM (Member State Legislation)**
Plastics Regulation 10/2011	Adhesives Coatings and Varnishes Printing Inks Rubber Paper and Board Textiles	Germany: Recommendation XXV Holland: Warenwet Chapter X

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